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# The So-Called Vinyl Chloride Disease

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# THE SO-CALLED VINYL CHLORIDE DISEASE
[Ueber die sogenannte Vinylchlorid-Krankheit]

by

S. Jühe, C.-E. Lange, G. Stein, and G. Veltman
Bonn University Dermatology Clinic

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Since the first reports on impairments of health of workers in the vinyl chloride (VC) industry appeared in 1958 [10], and of workers in the polyvinyl chloride (PVC) industry in 1963 [25], attention has been repeatedly directed at this branch of the chemical industry by further reports [3,4,7,8,12,28]. A syndrome was observed which was similar in its skin and bone changes to scleroderma, while its etiology and pathogenesis remained unresolved. Its principal symptom was the Raynaud syndrome -- nodose or surface hard skin changes and band-shaped osteolyses of the finger end-phalanges.

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We reported the first observations of this disease pattern in Germany in 1972 [15,16,17]. Since the clinical picture was initially reminiscent of a special form of progressive scleroderma, we subjected all the workers to a thorough internal examination, to determine whether there was visceral involvement in this case as well. We have recently made an exhaustive report [18] on the results obtained through the end of 1972, results which reveal new aspects in the assessment of the disease, and -- we believe -- should provide new stimuli for further research. Here we will summarize the most important features.

The 13 workers studied from April to December 1972 were 29 to 52 years old (average age: 39), and had worked for at least two, and as many as 18 years (average: 7 years) in a PVC-producing factory in various capacities, but predominantly as autoclave cleaners. The first symptoms of the disease appeared 1-1/2 to 3-1/2 years after beginning of employment in 11 patients, and after 7 and 11 years in two patients.

Symptoms and Findings

The most frequent first symptoms in the case histories are increased cold-sensitivity in the hands and feet, a feeling of numbness, and formication paresthesias. Also observed were tenderness in individual digital pulps, thickening of the end phalanges, and loosening of the nails, as well as such general complaints as severe fatigue, slowness, and forgetfulness, syncope-like dizziness, nausea at work, increased sweating, and upper abdominal complaints.

The skin changes play an important role in the diagnostics of the syndrome: Seven patients exhibited finger end-phalanges thickened like drumsticks (clubbed distension and shortening, watch-glass nails,

shortening of the nail body). In eight patients, we observed scleroderma-like skin changes: small nodose or more plate-like, very hard, relatively sharply delineated infiltrates, usually raised somewhat above the level of the skin, on the backs of the hands, the distal third of the flexor side of the forearm, and the cheek area. Three patients had no clinical skin changes.

The histological findings from biopsies (right or left hand) from all patients were relatively uniform. Apart from hyperorthokeratosis and epidermal atrophy, we also detected increases in size and number of capillaries in the upper cutis, increases in size and number and homogenization of collagenous bundles, and a marked rarefaction and fragmentation of the elastic fibers. The histological changes in the epidermis and the collagenous connective tissue are reminiscent of the edematous to infiltrative stages of progressive scleroderma. However, they can be clearly distinguished from the latter by the sometimes very pronounced damage to the elastic fibers and the vascular changes.

Circulatory disorders are the most frequent symptom. Nine of the 13 patients complained of them, and eight even gave these complaints as the first symptom. The scale of severity ranged from increased cold-sensitivity and acrocyanosis to the Raynaud syndrome (four patients). The circulatory disorders could be studied on an objective basis with the aid of temperature measurements, determination of the temperature recovery time after exposure to cold, capillary microscopy, and arm-hand arteriography. Oscillography and plethysmography did not yield any clearly pathological findings in any of the patients, so that it can be inferred that the cause of the circulatory disorders must be sought in

the periphery and not in the large vessels. This conclusion is supported by the angiographic and capillary-microscopic findings: In four patients with cold-sensitivity, ampulliform enlargements of the capillaries were detected in the nail-fold, as described in the Raynaud syndrome [14]. All seven patients who underwent arteriography exhibited pathological vascular pictures. The changes ranged from slight constriction of the arteriae digitales palmares propriae et communes with isolated, segmentally localized stenoses to major stenoses and segmental occlusions, sometimes even failure of the arteries to fill over the entire length of the fingers, and marked constriction in the palmar arches as well. According to the studies, there appears to be a direct relationship between the duration of exposure and the extent of the vascular damage.

The most conspicuous radiological finding in this disease is the band-shaped osteolyses between the processus unguicularis and the phalangeal shaft in individual or all fingers of six patients. In addition, fragmentations and marginal defects of the processus unguiculares were observed in six patients. In the bone changes as well, different degrees of severity could be distinguished: In milder cases, only a narrow lytic zone is visible, while in the advanced stage, the phalangeal shaft is almost completely destroyed, and the processus unguicularis rests on the base of the phalanx like a hood. The findings indicate that complete recovery of the bone cannot be anticipated [23,24]. It is noteworthy that there is a firm correlation between acroosteolyses and clubbed distension of the end phalanges. Hence, the "drumstick fingers" are a manifestation of the lytic bone process and not a symptom of an internal disease.

The study of the hematogenic system and blood clotting drew our attention to a noteworthy finding: All 13 patients exhibited a thrombopenia, ranging from mild to severe. The thrombocyte counts were repeatedly found to be between 30,000 and 119,000/µl (lower limit of normal = 150,000/µl). The sternal puncture performed on six patients to explain this finding yielded no indications, in any of the cases, of a disturbance of thrombocytopoiesis, osteomyelofibrosis, or osteomyelosclerosis. The remaining studies pointed to a mild reticulocytosis in eight patients (between 16 and 26 per thousand) and a mild leukopenia in five patients (2350 to 3950 leukocytes/µl), but no other major deviations from normal. The reticulocytosis and the leukopenia may be results of the splenomegaly found in 12 patients. No explanation has yet been found for the thrombopenia, although it is likely that a metabolic disturbance or increased catabolism in the periphery is involved.

In reviewing the case histories, it was notable that three patients complained of recurrent pains in the left epigastrium, and one patient reported pain in the right epigastrium and a sensation of fullness, but there were no reports of previous diseases of the liver or the spleen, prolonged use (ingestion) of medications, or heavy consumption of alcohol. Nevertheless, three patients without scleroderma-like skin changes or acroosteolyses exhibited, in their case histories, signs of chronic liver disease (bleeding from esophageal piles, splenorenal anastomosis; portal hypertension; esophageal piles, splenomegaly). Bromsulfalein retention was markedly increased, while there was nothing particularly striking about the values for serum transaminases and phosphatases. This discrepancy was also detected in the other ten patients. Four patients

had esophageal piles, and splenomegaly was found scintigraphically in twelve of the patients. The laparoscopy and liver-biopsy findings, which we had obtained for five patients by the end of 1972, showed conspicuous agreement: fine or pronounced waviness in liver surface, capsular fibrosis, increased marking of blood and lymph vessels, histologically a mild to marked fibrosis of portal fields and individual cell necroses, and mild coarse-grained fatty degeneration. These findings, which we were subsequently able to corroborate [19], suggest to us the following hypothesis: Apart from mild toxic changes in liver cells, an increase in connective tissue in the portal fields produces diffuse circulatory disorders in the liver and, in advanced stages, an intrahepatic block (which is quite conceivable as a presinusoidal block due to the obstacle at the level of the portal fields) with esophageal piles. The question of whether the splenomegaly is a secondary effect or whether this finding is also based on primary toxic changes has yet to be resolved.

In the checks on lung function (case history, X-ray examination, rest spirometry, entire-body plethysmography, blood-gas analysis), nine patients showed signs of predominantly restrictive changes, and there was a partial insufficiency in eight of the patients. Further investigations will be required to determine whether these disturbances are due to changes taking place in the lungs similar to those in collagenous and elastic connective tissue of the skin, i.e. based on incipient diffuse lung fibrosis.

The Triggering Factor

This is an occupation-related syndrome, the primary symptoms of which are (in order of frequency) thrombopenia, splenomegaly, toxic liver damage, disturbances of ventilation, circulatory disorders, and skin and bone changes. This complex of symptoms cannot be assigned to any previously known syndrome. The etiology and pathogenesis remain unresolved.

Is it possible to gain any insight into the etiology and pathogenesis by comparing our results with those known from the literature? What might be the triggering factor?

Liquid vinyl chloride polymerizes upon addition of water and numerous different additives, selected on the basis of the properties of the desired plastic. In this process, the temperature and pressure are raised, and polyvinyl chloride is produced. Regardless of the types of additives, a Raynaud syndrome and acroosteolyses have been found among autoclave cleaners in various countries. These symptoms appeared so characteristic that they resulted in recent years in the designation of the disease as "occupational acroosteolysis," and required diagnosis [28]. There is no reason to believe that the additives, which vary by country and method of production, play any significant role, even though harmful combination effects produced by these additives cannot be ruled out. Hence, the vinyl chloride, the substance present in the greatest amount, will be the focus of interest. The monomer vinyl chloride is first pumped through a closed system into the autoclaves. However, there are possibilities for gas to escape -- and thus to be inhaled -- at many points within the production process:

1. Leaks in the autoclave (inlets and outlets) during polymerization and in recovery processes;

2. In draining and opening the autoclaves and in drying the finished polyvinyl chloride. The residual gas consists of up to 90% vinyl chloride [6], and frequently causes leaden fatigue and brief disorientation in the workers;

3. From the cavities in the polymer precipitated on the inner wall of the reactor [5].

From the technical point of view, therefore, it is altogether possible that vinyl chloride is responsible for the syndrome discussed here.

Some facts have already been established concerning the effects of vinyl chloride on human and animal organisms. Its narcotic effect has been known for a long time [22]. Since 1958, there have been repeated reports of angioneurotic disturbances, including the Raynaud syndrome, among the workers in the polyvinyl chloride industry [1,10,21]. There are isolated references in the literature to intoxications with vinyl chloride, with symptoms including reversible vertigo, mild to pronounced drowsiness, disorientation, skin manifestations such as in a second-degree burn, and reduced blood clotting [6,9,11]. One worker died as a consequence of the poisoning.

Pulmonary edema, vascular congestion in the lungs, liver, and kidneys, and diminished blood clotting have been established as consequences of acute vinyl chloride intoxication in animal experiments [20]. Centrolobular degeneration and necroses with frothy vacuolation as well as periportal cell infiltration were produced in the liver in prolonged experiments [26].

Recently, skin, lung, and bone tumors and disturbances in formation of bone have been reported [27]. These animal-experiment findings resulted in another reduction in 1970 of the maximum place-of-work concentration to 100 ppm [13]. We have not heard of any regular gas-concentration measurements at places of work.

The symptoms described as part of this disease -- Raynaud syndrome, toxic liver changes, disturbances of bone formation, and prenarcotic syndrome -- may thus be triggered by vinyl chloride, so that, in view of the situation at the job sites, we may express the urgent suspicion that prolonged exposure to vinyl chloride is at least one, if not the cause of the disease. Moreover, since the syndrome acquires the character of a systemic disease due to the involvement of a large number of organs, and since the term "occupational acroosteolysis" refers only to a symptom which is certainly not crucial for the prognosis, we have suggested the designation "so-called vinyl chloride disease."

## Pathogenesis

The pathogenesis is still unexplained. However, based on our findings, we conjecture that the disease as a pathogenetic principle in the widest sense is a consequence of a disturbance of the connective tissue or vascular connective tissue. Evidence for the view that the toxic agent acts not only through inhalation, but also percutaneously, are the facts that only unclothed parts of the head show scleroderma-like changes and that the band-shaped osteolyses were found only on the end phalanges of the fingers. Both scleroderma-like skin changes and acroosteolyses were observed only in workers involved for long periods

in cleaning autoclaves, which can perhaps be explained by the fact that 600-1000 ppm vinyl chloride has been measured in the vicinity of the autoclave wall [5]. We viewed the qualitative and quantitative changes in the collagenous and elastic connective tissue of the skin, the increase in number of collagenous fibers in the portal fields of the liver, the increases in number and size of capillaries in the upper cutis detected histologically and by capillary microscopy, and the clinically, angiographically, and thermographically detectable peripheral circulatory disorders all as indications of an underlying disturbance of connective tissue. Moreover, the changes in the bone (osteolyses as a consequence of trophic disturbance due to damage to the vasa nutricia) and in the lung (restrictive and obstructive ventilation disturbances) could be interpreted in the same sense. The prognosis for the disease -- up until now assessed quite optimistically in the literature -- appears serious to us in view of the thrombopenia, splenomegaly, and portal hypertension. According to our observations, another reason for a conservative prognosis is the bone changes.

## Consequences for Practice

The triad of systemic disease, serious prognosis, and relatively high morbidity (according to our investigations, certainly greater than 10%) in predominantly young men impels us to make the following strong recommendations:

1. Series of studies on epidemiology and preventive medicine should be carried out. In our opinion, it is not sufficient just to look for the Raynaud syndrome, nodose skin changes, and band-shaped osteolyses, since

these symptoms, no matter how characteristic, characterize the advanced stage of the disease. Instead, a thrombocyte count should be taken at regular time intervals for all workers in PVC plants, so that workers with a constant thrombopenia -- it appears to be the first objectivizable symptom -- can be removed from this area without waiting for much more serious internal findings.

2. Workers with liver diseases or circulatory diseases should not be engaged.

3. Gas concentrations should be measured regularly at various locations in the plant, in order to avoid exceeding the maximum place-of-work concentration. Also desirable are engineering improvements with the objective of automating the process as much as possible and improving ventilation conditions, in order to reduce the possibilities of inhaling the gases to a minimum.

4. Workers already afflicted with the disease should receive compensation, and the disease should be recognized as an occupational disease requiring compensation, by including it in the BKVO [Occupational Disease Ordinance] list.

5. Further animal experiments with vinyl chloride are also necessary, with special attention to the skin, bone, lung, liver, and spleen.

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